

The Survey on Cellular and Engineered Tissue Therapies in Europe in 2009

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Thanks to the coordinated efforts of four major scientific organizations, this report describes the “novel cellular therapy” activity in Europe for the year 2009. Fifty teams from 22 countries reported data on 814 patients using a dedicated survey, which were combined to additional 328 records reported by 55 teams to the standard European group for Blood and Marrow Transplantation (EBMT) database. Indications were cardiovascular (37%; 64% autologous), graft-vs.-host disease (27%; 7% autologous), musculoskeletal (17%; 98% autologous), epithelial/parenchymal (8%; 73% autologous), autoimmune (9%; 84% autologous), or neurological diseases (3%; 50% autologous). Autologous cells were used predominantly for cardiovascular (42%) and musculoskeletal (30%) disorders, whereas allogeneic cells were used mainly for graft-vs.-host disease (58%) and cardiovascular (30%) indications. Reported cell types were mesenchymal stem/stromal cells (MSC) (46%), hematopoietic stem cells (27%), chondrocytes (7%), keratinocytes (5%), dermal fibroblast (13%), and others (2%). In 59% of the grafts, cells were delivered after expansion; in 2% of the cases, cells were transduced. Cells were delivered intraorgan (46%), on a membrane or gel (29%), intravenously (16%) or using 3D scaffolds (8%). As compared to last year, the number of teams adopting the dedicated survey was 1.7-fold higher, and, with few exceptions, the collected data confirmed the captured trends. This year’s edition specifically describes and discusses the use of MSC for the treatment of autoimmune diseases, due to the scientific, clinical, and economical implications of this topic.

Introduction

IN 2008, THE EUROPEAN SECTIONS of the Tissue Engineering and Regenerative Medicine International Society (TERMIS-EU), of the International Society of Cellular Therapy (ISCT-Europe), and of the International Cartilage Repair Society (ICRS) have for the first time coordinated a joint initiative with the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR) to establish a comprehensive, quantitative map of patients being treated in Europe by the so-called “novel cellular therapies,” namely, the use of nonhematopoietic stem cells (HSC) or of HSC for non-hematological indications. The first activity report, published last year,¹ was an extension of the well-established EBMT annual report, an instrument to observe trends and to monitor changes in the use of HSC transplants for the

treatment of hematologic disorders in Europe.^{2,3} The activity survey does not provide any data on specific protocols, outcome, age, or sex of patients or their pre- and post-transplant therapy. The goal of the data collection is the rapid dissemination of the status in the field of novel cellular therapies, identifying trends related to covered indications, as well as specific cell types, cell processes, and delivery modes used. Long-term analyses of the EBMT survey provided evidence that the instrument can foresee trends with high predictability and very rapidly (e.g., the increasing use of cord blood as a stem cell source, the change from bone marrow to peripheral blood or the utilization and integration of unrelated donor transplants^{4,5}) and can thus provide a formal basis for patient counseling and healthcare planning.

In this article, we report the results of the second survey for the activity in 2009, with a direct comparison to the 2008

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data reported last year and specifically discussing the use of mesenchymal stem/stromal cells (MSC) for the treatment of autoimmune diseases.

Patients and Methods

Data collection and validation

Participating teams were requested to report their data for 2009 by indication, cell type and source, donor type, processing method, and delivery mode. The survey followed the

traditional principles of the EBMT, concentrating on numbers of patients with a first cellular therapy. For EBMT teams not using the full questionnaire, information on cellular therapies was limited to numbers of HSC for non-hematopoietic use, MSC-based therapies (later identified to be almost exclusively related to treatment of graft-vs.-host-disease), and donor type. Questionnaires were collected by paper forms or electronically. Quality control measures, for EBMT members only, included several established independent systems: confirmation of validity of the entered data

TABLE 1. NUMBER OF CELLULAR THERAPY TRANSPLANTS FOR NOVEL CELLULAR THERAPIES (I.E., FOR NONHEMATOPOIETIC INDICATIONS OR USING NONHEMATOPOIETIC CELLS) IN EUROPE 2009 SORTED BY INDICATION, CELL SOURCE, AND DONOR TYPE

Indication	Cell type and source										Total	
	Autologous					Allogeneic						
	HSC	MSC	Chondrocyte	Keratinocyte	Other	HSC	MSC	Fibroblast	Other	Autologous		Allogeneic
Cardiovascular												
Peripheral artery disease	36	20								56	0	56
Cardiomyopathy	11	1								12	0	12
Heart failure	21	12								33	0	33
Myocardial ischemia	109	2								111	0	111
Bypass graft	14	2								16	0	16
Ulcer								100		0	100	100
Other/unspecified	38 ^a							50		38	50	88
Musculoskeletal										0	0	0
Bone repair (maxillofacial)	1						1			1	1	2
Bone repair (orthopedics)	23	43				2				66	2	68
Osteogenesis imperfecta	1									1	0	1
Cartilage repair		9	82							91	0	91
Muscle repair										0	0	0
Tendon/ligament	5									5	0	5
Reconstructive surgery	1									1	0	1
Other/unspecified	7 ^a	17								24	0	24
Neurological										0	0	0
Parkinson's										0	0	0
Peripheral nerve regeneration (trauma)										0	0	0
Other/unspecified	9 ^a				8	14 ^a	3			17	17	34
Epithelial										0	0	0
Skin reconstruction				51						51	0	51
Cornea repair					3				24	3	24	27
Organ failure	10									10	0	10
Diabetes										0	0	0
Liver insufficiency	2									2	0	2
Other										0	0	0
Autoimmune										0	0	0
Neurological		80								80	0	80
Rheumatological		1					1			1	1	2
Gastrointestinal		3					2			3	2	5
Other		3					13			3	13	16
Graft vs. host disease		21 ^a					286 ^a			21	286	307
Total	288	204	82	51	11	16	306	150	24	646	496	1142

^aThese numbers were imported from the limited questionnaire included in the standard EBMT survey sheet.

HSC, hematopoietic stem cells; MSC, mesenchymal stromal/stem cells; EBMT European group for Blood and Marrow Transplantation.

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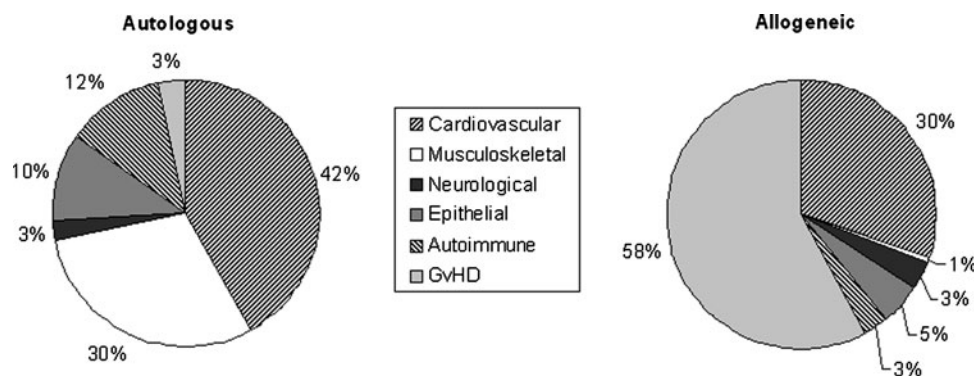


FIG. 1. Percentage of indications for novel cellular therapies in Europe in 2009, sorted by donor type. Data used for this chart were derived from the extended questionnaire and the standard European group for Blood and Marrow Transplantation (EBMT) survey sheet.

by the reporting team, selective comparison of the survey data with MED-A data sets in the EBMT ProMISE data system, cross-checking with the National Registries and onsite visits of selected teams. No quality control system could be applied for the non-EBMT reporting teams yet.

Teams

Members of the four participating societies from 47 countries (39 European and 8 affiliated countries) were contacted for the 2009 report (EBMT survey). The non-European countries affiliated with the EBMT were Algeria,

TABLE 2. NUMBER OF CELLULAR THERAPY TRANSPLANTS FOR NOVEL CELLULAR THERAPIES IN EUROPE 2009 SORTED BY CELL PROCESSING MODE

Indications	Cell processing					
	Nonexpanded	Expanded	Untransduced	Transduced	Unsorted	Sorted
Cardiovascular						
Peripheral artery disease	42	14	56		50	6
Cardiomyopathy	11	1	12		12	
Heart failure	21	12	33		17	16
Myocardial ischemia	109	2	104	7	102	9
Bypass graft	14	2	16		4	12
Valve replacement						
Ulcer		150	150		150	
Other	23		23		23	
Musculoskeletal						
Bone repair (maxillofacial)	1	1	2		2	
Bone repair (orthopedics)	57	11	67	1	67	1
Osteogenesis imperfecta	1		1			1
Cartilage repair	6	85	91		91	
Muscle repair						
Tendon/ligament	5		5		5	
Reconstructive surgery	1		1		1	
Other		17	17		17	
Neurological						
Parkinson's						
Peripheral nerve regeneration						
Other	5	11	13	3	5	11
Epithelial						
Skin reconstruction		51	51		51	
Cornea repair	24	3	27		27	
Organ failure	10		10			10
Diabetes						
Liver insufficiency		2		2	2	
Other						
Autoimmune						
Neurological		80	80		80	
Rheumatological		2	2		2	
Gastrointestinal		5	5		5	
Other		16	16		16	
Graft vs. host disease		19	19		19	
Total	330	484	801	13	748	66

Data only from extended questionnaire.

Iran, Israel, Jordan, Lebanon, Saudi Arabia, South Africa, and Tunisia. Eighty teams in 22 countries (20 European and 2 affiliated countries) reported novel cellular therapies using the survey form, with detailed information on indication, cell source and type, donor type, processing, and delivery mode. Thirty of the 80 teams reported that no cellular therapies had been performed in 2009. An additional 84 teams from 16 countries (14 European and 2 affiliated country) reported using the standard EBMT transplant activity survey, allowing to include only limited information. Of these 84 teams, 29 reported that no cellular therapies were performed in 2009. Teams that responded with activity are listed in the Appendix in alphabetical order by country, city, and EBMT centre code (if applicable), along with the total numbers of reported cellular therapies. There were no cellular therapies (including HSC transplants) reported to the survey from Albania, Algeria, Andorra, Armenia, Azerbaijan, Bosnia-Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Georgia, Iceland, Ireland, Jordan, Latvia, Liechtenstein, Lithuania, Luxembourg, Macedonia, Malta, Moldavia, Monaco, Montenegro, Romania, San Marino, Saudi Arabia, South Africa, Tunisia, and the Ukraine in 2009.

Transplant rates

Transplant rates, defined as numbers of cellular therapies per 10 million inhabitants, were computed for each country, without adjustments for patients who crossed borders or received treatment in a foreign country. Population numbers were obtained from the U.S. census office database (www.census.gov).

Results

Number of novel cellular therapies and disease indications

T1► According to the received reports, a total of 1142 patients were treated with novel cellular therapies, 496 (43%) with allogeneic and 646 (57%) with autologous cells (Table 1). Main indications were cardiovascular disorders (37%; 64% autologous), graft-vs.-host disease (27%; 7% autologous), musculoskeletal disorders (17%; 98% autologous), autoimmune diseases (9%; 84% autologous), and epithelial (8%; 73% autologous) and neurological disorders (3%; 50% autologous).

From 814 patients, more detailed information was obtained concerning indications. Among the cardiovascular disorders, decubitus and leg ulcers ($n=150$), myocardial ischemia ($n=111$), peripheral artery disease ($n=56$), and heart failure ($n=33$) were the most frequently reported indications. Among the musculoskeletal disorders, cartilage repair ($n=91$) and bone repair ($n=68$) were the main reason for a cellular therapy. Skin reconstruction ($n=51$) and cornea repair ($n=27$) were the two main reported indications for epithelial/parenchymal disorders. Neurological indications were only performed for disorders not included in the form ($n=16$, 8 of which for glioblastoma). Among autoimmune disorders, neurological diseases ($n=70$), including multiple sclerosis, represented the predominant indication. The number of reports of patients treated for GvHD ($n=19$) needs to be combined with that reported in the EBMT standard form, for a total of 307 cases (Table 1).

Cell type, source, and donor type

Of the 304 HSC treatments, 95% were autologous transplants and 80% were used to treat cardiovascular diseases (Table 1). All 82 chondrocyte and 51 keratinocytes transplants were autologous and the 150 dermal (100 of which of fetal origin) fibroblasts transplants were allogeneic. Of the 520 MSC based therapies, 59% were allogeneic. The donor type was associated with the disease indication: autologous cells were used predominantly for cardiovascular (42%) and musculoskeletal (30%) disorders, whereas allogeneic cells

TABLE 3. NUMBER OF CELLULAR THERAPY TRANSPLANTS FOR NOVEL CELLULAR THERAPIES IN EUROPE 2009 SORTED BY DELIVERY MODE

Indications	Cell delivery mode				Total
	<i>i.v.</i>	Intraorgan	Membrane/ gel	3D	
Cardiovascular					
Peripheral artery disease	3	53			56
Cardiomyopathy		12			12
Heart failure		33			33
Myocardial ischemia	47	64			111
Bypass graft		16			16
Valve replacement					
Ulcer			150		150
Other	23				23
Musculoskeletal					
Bone repair (maxillofacial)		1		1	2
Bone repair (orthopedics)		22		46	68
Osteogenesis imperfecta		1			1
Cartilage repair		60	11	20	91
Muscle repair					
Tendon/ligament		5			5
Reconstructive surgery	1				1
Other		17			17
Neurological					
Parkinson's					
Peripheral nerve regeneration					
Other	3	13			16
Epithelial					
Skin reconstruction			51		
Cornea repair			27		27
Organ failure		10			10
Diabetes					
Liver insufficiency	2				2
Other					
Autoimmune					
Neurological		80			80
Rheumatological	2				2
Gastrointestinal	5				
Other	13	3			16
Graft vs. host disease	19				19
Total	118	390	239	67	814

Data only from extended questionnaire.
i.v., intravenous.

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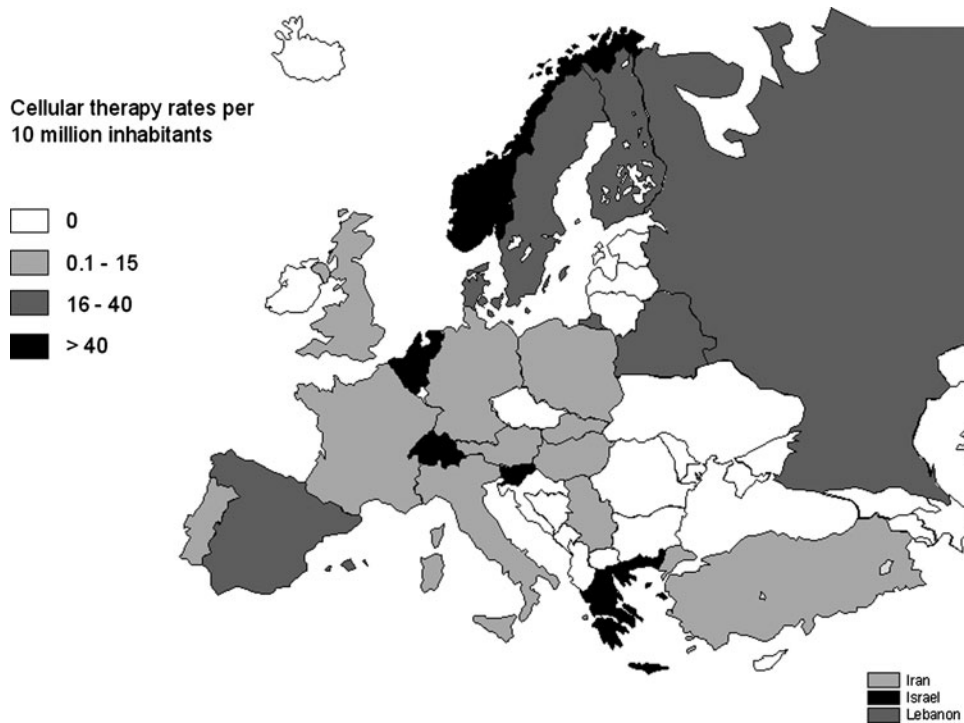


FIG. 2. Cellular therapy rates (number of cellular therapies per 10 million inhabitants) for novel cellular therapies in Europe in 2009. Data used for this chart were derived from the extended questionnaire and the standard EBMT survey sheet.

F1 ► were used mainly for graft-vs.-host disease (58%) and cardiovascular (30%) indications (Fig. 1). In the detailed survey, MSC were obtained from bone marrow in 219 (94%) cases and mostly used to treat autoimmune (53%), musculoskeletal (31%), and cardiovascular disorders (14%). For the 264 HSC treatments, cells were derived from the bone marrow (85%), peripheral blood (8%), placenta (5%), or unspecified cell source (2%).

Cell processing and delivery mode

Of all the grafted products reported in detailed form, 59% were based on expanded cells and in 2% of the cases cells were transduced (Table 2). About one half (48%) of the products was given intraorgan, 29% on a membrane or gel, 14% intravenously, and 8% using a 3D scaffold. Non-expanded cells were used to treat 55% of cardiovascular, 38% of musculoskeletal, 38% of epithelial/parenchymal, and 31%

◀ T2



FIG. 3. Number of teams reporting novel cellular therapies in Europe in 2009 per 10 million inhabitants. Data used for this chart were derived from the extended questionnaire and the standard EBMT survey sheet.

of neurological disorders, whereas autoimmune diseases were exclusively treated with expanded cells. Cell sorting was operated for 69% of neurological, 11% of epithelial, 11% of cardiovascular, and 1% of musculoskeletal disorders. Beyond a few sporadic exceptions, reported for cardiovascular, musculoskeletal, and neurological diseases, transplanted cells were not genetically transduced.

T3 ▶ For neurological and autoimmune applications, cells were delivered exclusively intravenous or intraorgan (Table 3). The use of a membrane or a gel for cell delivery was reported mainly for cardiovascular treatments (63%), epithelial/parenchymal treatments (33%), or for cartilage repair (5%). For the group of musculoskeletal indications, all possible cell delivery modes were reported, with a predominant tendency for intraorgan (57%) and for the use a 3D scaffold (36%).

Transplant rates and active teams

F2 ▶ Reported cellular therapies were performed in a limited number of countries and with different intensity. Figure 2 displays the cellular therapy transplant rates per 10 million inhabitants in the different European & EBMT-associated countries. High transplants rates (i.e., 40 per 10 million population) were reported in Belgium, Greece, Israel, the Netherlands, Norway, Slovenia, and Switzerland. The number of teams reporting cellular therapies was also mapped in the different European & EBMT-associated countries after normalization to the inhabitant numbers (Fig. 3). The number of active teams per 10 million inhabitants was higher than 4 in Belgium, Greece, Israel, Lebanon, and Slovenia.

Discussion

The intersociety program of the survey on novel cellular therapies represents a unique opportunity for early access to

information that integrates that available in public databases (e.g., www.clinicaltrial.gov) and that will only partially and at later times be published in the scientific literature. The 1.7-fold increase in the number of participating teams within Europe and associated countries as compared to the past year demonstrates the raising interest in the program and is expected to stimulate the contribution by other groups and societies in the next years. In this regard, the list of reporting centers in the manuscript Appendix is far from being exhaustive of the effective status, but has the potential to become a key reference for the field.

As compared to the data collected for patients treated in the previous year,¹ the present report confirms the main identified trends, though with few remarkable differences, especially related to the cardiovascular diseases. For the latter indications, the number of total treated cases increased by 1.4-fold, with a 7.0-fold higher percentage for peripheral artery disease and a 1.7-fold lower percentage for myocardial ischemia. In the same category of cardiovascular disorders, the cell source shifted from entirely autologous to allogeneic in 36% of the cases, with an increase from 8% to 45% in the use of expanded cells and the introduction of a membrane or gel delivery vehicle in 37% of the treatments. The changing variety of approaches tested may be considered as a sign that several key issues still need to be addressed in that field, including the optimal cell type, source and dosing, the most effective route for cell transfer, and methods for enhancing survival of the cellular graft.⁶

The uniform category within those analyzed was the one targeting autoimmune disorders. The cells used were uniquely expanded MSC, untransduced, unsorted, and delivered intravenously (19%) or intraorgan (80%). The use of MSC in modulating autoimmune diseases is an emerging area of activity in cellular therapy.⁷ Based on positive animal model data and *in vitro* demonstration of an anti-

TABLE 4. REFERENCES TO THE WORLDWIDE PUBLISHED CLINICAL STUDIES ON THE TREATMENT OF AUTOIMMUNE DISEASES USING MESENCHYMAL STEM/STROMAL CELLS

Autoimmune disease	No. of patients	MSC source	Delivery route	Clinical outcome	Reference
Multiple sclerosis	10	Allogeneic bone marrow	Intrathecal	Mixed	Mohyeddin <i>et al.</i> ⁹
Scleroderma	1	Allogeneic bone marrow	i.v.	Improved	Christopeit <i>et al.</i> ¹⁰
Multiple sclerosis	1	Allogeneic umbilical cord	i.v.	Improved	Liang <i>et al.</i> ¹¹
Multiple sclerosis	3	Mixed allo & autologous fat	Mixed i.v. & Intrathecal	Improved clinic MRI unchanged	Riordan <i>et al.</i> ¹²
Crohns fistulae	14	Autologous fat	Intrafistula	71 % closure	Garcia-Olmo <i>et al.</i> ¹³
Scleroderma digital ulcer	2	Autologous blood & bone marrow	Local	Improved	Nevskaya <i>et al.</i> ¹⁴
Lupus nephritis	15	Allogeneic bone marrow	i.v.	Improved SLEDAI and proteinuria	Liang <i>et al.</i> ¹⁵
Lupus nephritis	16	Allogeneic umbilical cord	i.v.	Improved SLEDAI and proteinuria	Sun <i>et al.</i> ¹⁶
SLE	2	Autologous bone marrow	i.v.	No change	Carrion <i>et al.</i> ¹⁷
SLE alveolar hemorrhage	1	Allogeneic umbilical cord	i.v.	Improved	Liang <i>et al.</i> ¹⁸
Crohns disease	10	Autologous bone marrow	IVI	Improved	Duijvestein <i>et al.</i> ¹⁹
Multiple sclerosis	15	Autologous bone marrow	Intrathecal (all) plus IVI (5)	Some stabilized	Karussis <i>et al.</i> ²⁰
Amyotrophic lateral sclerosis	19	Autologous bone marrow	Intrathecal (all) plus i.v. (9)	No change	Karussis <i>et al.</i> ²⁰
Multiple sclerosis	10	Autologous bone marrow	Intrathecal	Mixed	Yamout <i>et al.</i> ²¹

SLE, systemic lupus erythematosus.

proliferative effect of MSC on immune competent cells, many groups have launched clinical trials (14 currently registered on clinicaltrials.gov), but no large prospective randomized data have been published. Small phase I studies and single case reports have been published (Table 4), most showing acceptable feasibility and safety and some early efficacy. No reports of acute toxicity have occurred, which makes MSC an attractive option as a therapeutic agent capable of homing to damaged or distressed tissue. The positive therapeutic effect seems to be exerted via multiple paracrine factors, since transdifferentiation into healthy regenerated tissue is not considered biologically relevant. The data collected in the survey confirm that sources of MSC are autologous (requiring local GMP facilities and associated quality management systems) or allogeneic (requiring dedicated companies offering screened MSC batches derived under tightly regulated processes from bone marrow, adipose tissue, placenta, or umbilical cord). Despite the source dependent phenotypic and functional MSC variations, all have been demonstrated to exert *in vitro* immunomodulatory effects. More data are urgently required concerning clinical efficacy, MSC fate after transplantation, and long-term safety, especially with regard to tumor surveillance. The generation of these data will be critical to make the transition from a correctly prudent and still scattered use of MSC for autoimmune diseases to the routine clinical implementation of consolidated and standardized protocols, compliant to the regulatory framework for Advanced Therapy Medicinal Products by the European Medicines Agency (www.ema.europa.eu).

The European program on novel cellular therapies is paralleled by similar initiatives in the United States, capturing the activity of 18 centers for a total of 115 treatments.⁸ Despite the inherent difficulties associated with the collection and management of data across different geographical areas, for the years to come efforts should be directed at coordinated initiatives toward the establishment of a global survey and report.

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Disclosure Statement

There are no conflicts of interest to declare. Writing of the article was the sole responsibility of the authors.

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Appendix: List of Reporting Novel Cellular Therapy Centers in Europe in 2009

List of reporting novel cellular therapy centers in Europe in 2009

Format: City, Hospital, Center Identification Code number (if data were imported from the standard EBMT survey sheet), Physicians (total treatments; allogeneic/autologous)

Austria

Graz, University of Graz, CIC 308, W. Linkesch (1; 1/0)

Vienna, Medical University Hospital, S. Marlovitis, Ch. Albrecht (5; 0/5)

Belarus

Minsk, Belorussian Center, CIC 591, O Aleinikova (15; 15/0)

Minsk, Hospital No. 9, N. Milanovich (2; 1/1)

Belgium

Antwerpen, University Antwerpen, CIC 996, W. Schroyens (6; 0/6)

Brugge, A.Z. St. Jan, CIC 506, D. Selleslag, A.v. Hoof, J.v. Droogenbroeck, K.v. Eygen (4; 4/0)

Brussels, Military Hospital Queen Astrid, Gilbert Verbeken (47; 0/47)

Leuven, University Hospital Gasthuisberg, CIC 209, G. Verhoef, M. Delforge, J. Maertens (7; 7/0)

Liège, University Hospital Sart-Tilman, CIC 726, Y. Béguin, B de Prijck (12; 12/0)

Brussels, U.L.B. Hôpital Erasme, CIC 596, B. Bailly, A. Kentos, M. Lambermont (2; 0/2)

Gent, University Hospital, CIC 744, L.A. Noens (2; 2/0)

Denmark

Aarhus, Amtssygehus, E. Segel, Dr. Moeller (2; 0/2)

Copenhagen, The Heart Centre Rigshospitalet, J. Kastrup (13; 0/13)

Finland

Helsinki, Helsinki University Central Hospital, CIC 515, L. Volin (12; 0/12)

France

Clermont Ferrand, CRCTCP, CHU Estaing, J.-O. Bay, F. Deméocq, P. Travade (37; 24/13)

Grenoble, Hospitalier A. Michallon, CIC 270, J.Y. Cahn, F. Garban, P. Drillat, D. Plantaz (2; 0/2)

Germany

Berlin, Universitäts-Klinik Benjamin Franklin, CIC 590, E. Thiel, L. Uharek (2; 2/0)

Dresden, Universitätsklinikum Carl Gustav Carus, Med. Poliklinik, G. Ehninger, H. Bornhäuser (4; 3/1)

Dresden, Universitätsklinikum Carl Gustav Carus, Hematology, CIC 808, G. Ehninger, H. Bornhäuser (22; 21/1)

Frankfurt, Universitätsklinikum d. J. W. Goethe, CIC 138, T. Klingebiel, P. Bader (3; 3/0)

Halle, Clinic Bergmannstrost, H.J. Meisel (14; 0/14)

Hannover, Medizinische Hochschule, CIC 295, A. Ganser, M. Eder (1; 1/0)

Köln, Universitäts-Klinik, CIC 534, M. Hallek, Ch. Scheid, F. Berthold, T. Simon (6; 0/6)

Tübingen, Medizinische Universitäts-Klinik (peds), CIC 535, R. Handgretinger, P. Lang (13; 12/1)

Ulm, Kinderklinik der Universität, CIC 204, W. Friedrich, K. Debatin (1; 1/0)

München, KK Munchen Schwabing, CIC 189, S. Burdach, A. Wawer, M. Nathrath (1; 1/0)

Mainz, Medizinische Klinik der Universität, CIC 786, K. Kolbe, D. Wehler (1; 1/0)

Heidelberg, Angelika Lautenschläger-Klinik, CIC 524, J. Greil (1; 1/0)

Ratingen, DRK Blutspendedienst West (6; 0/6)

Würzburg, Universitätsklinikum, P. Speer, P. Schlegel (1; 1/0)

Greece

Athens, Academy of Athens, A. Papassavas (37; 0/37)

Athens, Evangelismos Hospital, CIC 622, D. Karakasis, N. Harhalakis (2; 2/0)

Athens, Aghia Sophia Children's Hospital, CIC 752, S. Graphakos (2; 1/1)

Thessaloniki, Sports Clinic, Emanuel T. Papacostas (3; 0/3)

Athens, Aghia Sophia Children's Hospital, S. Graphakos (1; 0/1)

Hungary

Debrecen, University of Debrecen, Z. Boda, E. Rajnavolgyi (2; 0/2)

Iran, Islamic Rep.

Teheran, Shariati Hospital, CIC 633, M. Jahani (44; 36/8)

Teheran, Teheran University of Medical Sciences, M. Mohyeddin (49; 0/49)

Israel

Jerusalem, Hadassah University Hospital, CIC 258, R. Or, S. Slavin (34; 34/0)

Petach-Tikva, Beilinson Hospital, CIC 409, M. Yeshurun (1; 1/0)

Tel Hashomer, Chaim Sheba Medical Center, CIC 572, A. Toren (2; 2/0)

Tel Hashomer, Sheba Medical Center, CIC 754, A. Nagler, A. Shimoni, (6; 6/0)

Italy

Bologna, 6th div Rizzoli Orthopedic Institute, S. Giannini, R. Buda, E. Kon (5; 0/5)

Firenze, Policlinico di Careggi, CIC 304, A. Bosi, S. Guidi (2; 0/2)

Monza, Ospedale S. Gerardo, CIC 279, C. Uderzo (8; 8/0)

(Continued)

Appendix: (continued)

Piacenza, Ospedale Civile, CIC 163, L. Cavanna (14; 0/14)
 Reggio di Calabria, Azienda Ospedale "Riuniti e Morelli," Bianchi- Melacrino, CIC 587 P. Iacopino (3; 0/3)
 Udine, Policlinico Universitario & General Hospital, CIC 705, A. Sperotto, R. Fanin (1; 0/1)
 Brescia, Università degli Studi di Brescia, CIC 741, F. Porta (1; 1/0)
 Genova, Istituto Giannina Gaslini, CIC 274, G. Dini, E. Lanino (1; 1/0)
 Bergamo, Ospedale Riuniti, CIC 658, A. Rambaldi (2; 2/0)
 Pavia, Policlinico IRCCS St. Matteo, CIC 557, M. Zecca (2; 2/0)
 Bologna, Istituto Oropedico Rizzoli, L. Roseti (9; 0/9)
 Milano, IRCCS Galeazzi Orthopedic Institute, M. Moretti, P. Volpi, H. Schoenhuber (5; 0/5)
 Piemonte, Ospedale degli infermi di Biella, A. Siclari (34; 0/34)

Lebanon
 Beirut, American University of Beirut, A. Bazarbachi (4; 0/4)
 Beirut, American University Medical Centre, B. Yamout (10; 0/10)

Netherlands
 Leiden, University Hospital, CIC 203, R. Willemze, M. Egeler (70; 24/46)
 Utrecht, University Hospital, E. Petersen, N.M. Wulffraat, I. Slaper (24; 0/24)
 Rotterdam, Erasmus University Medical Center, Wim J. van der Giessen (6; 0/6)
 Groningen, University Hospital, CIC 546, G. van Imhoff, (1; 1/0)
 Maastricht, University Hospital, CIC 565, H.C. Schouten, J. Wagstaff (1; 1/0)
 Amsterdam, Academic Med Centre, CIC 247, M.J. Kersten, J. Zsiros (3; 3/0)

Norway
 Oslo, University Hospital Rikshospitalet, J. Brinchmann (22; 0/22)

Poland
 Cracow, University Children's Hospital JUMC, CIC 507, J. Gozdzik (9; 0/9)
 Wroclaw, Lower Silesian Cent./BM Donor Registry, A. Lange (2; 0/2)

Portugal
 Lisbon, Instituto Portugues de Oncologia, CIC 300, M. Abecasis (3; 3/0)

Russian Fed.
 Moscow, Russian Children's Hospital, CIC 694, A. Maschan, E. Skorobogato, E. Pachanov (15; 15/0)
 Moscow, Cancer Research centre, G. Mentrevich (14; 14/0)
 Moscow, Research Haematology Center of RAS, V.G. Savtchenko (9; 9/0)
 Novosibirsk, Inst. Clinical Immunology, CIC 376, I. Lisukov (20; 2/18)
 St. Petersburg, Pavlov Medical University, B.V. Afanassiev, L. Zubarovskaya (180; 150/30)
 St. Petersburg, Pavlov Medical University, CIC 725, B.V. Afanassiev, L. Zubarovskaya (2; 2/0)

Serbia
 Belgrade, Military Medical Academy, D. Stamatovic (7; 0/7)

Slovak Republic
 Bratislava, National Cancer Institute, CIC 560, J. Lakota (1;1/0)

Slovenia
 Ljubljana, University Medical Centre, CIC 640, J. Pretnar (10; 0/10)

Spain
 Barcelona, Hospital Clinic, CIC 214, E. Carreras (4; 4/0)
 Cordoba, Hospital Reina Sofia, A. Torres-Gomez (32; 0/32)
 Madrid, Hospital La Paz, CIC 734, A. Martinez, A. Sastre, R. Arrieta (2; 0/2)
 Murcia, Hospital Virgen de la Arrixaca, JM. Moraleda, A. Morales Lazaro (9; 3/6)
 Palma de Mallorca, Hospital Son Dureta, CIC 722, J. Besalduch, M. Canaro (4; 0/4)
 Pamplona, Clinica Universitaria de Navarra, CIC 737, J. Rifon (1; 1/0)
 Salamanca, Complejo Hospital, CIC 727, D. Caballero (9; 9/0)
 Murcia, Hospital General Universitario Morales Meseguer, CIC 735, V. Vicente-Garcia, I. Heras (3; 0/3)
 Barcelona, ITRT Inst. de Terapia Regenerativa Tissular, C.M. Teknon (15; 0/15)
 Madrid, Hospital Universitario San Carlos, J. Diaz-Mediavilla, L. Llorente, R. Martinez (5; 0/5)
 Madrid, Hospital General La Paz (adults), R. Arrieta (3; 0/3)

Sweden
 Lund, University Hospital, CIC 283, S. Lenhoff (5; 5/0)
 Stockholm, Karolinska University Hospital, Huddinge, CIC 212, P. Ljungman (14; 12/2)

Switzerland
 Geneva, Hôpital Cantonal Universitarie, CIC 261, J. Passweg, Y. Chalandon, M. Ansari (10; 0/10)
 Lugano, Cardiocentro Ticino, G. Astori (23; 0/23)

Turkey
 Adana, Baskent University Adana, H. Ozdogu, C. Boga, S. Asma, S. Yuce (1; 1/0)

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Appendix: (continued)

Ankara, Ihsan Dogramaci Children's Hospital (Hacettepe), CIC 399, A. Tuncer, D. Uckan (6; 5/1)
Istanbul, University of Istanbul, CIC 760, D. Sargin, S. Kalayoglu-Besisik (1; 1/0)
Antalya, Medical Park Hospitals, CIC 919, Y. Koc (3; 3/0)
Ankara, Gazi University, Besevler, CIC 169, G. Sucak (3; 3/0)

United Kingdom

Manchester, Royal Children's Hospital, CIC 521, R. Wynn (1; 1/0)
London, University College Hospital, CIC 224, K. Thomson, (1; 1/0)
London, Hammersmith Hospitals NHS Trust, CIC 205, J. Apperley, E. Olavarria, E. Kanfer, A. Rahemtulla, R. Szydlo (3; 3/0)
London, Great Ormond Street Hospital, CIC 243, P. Veys, (7; 7/0)
London, St. Bartholomew's and the Royal London Hospital, CIC 768, J. Gribben, J. Cavenagh, S. Agrawal,
T. Lister (14; 0/14)
Oswestry, Oswestry Orthopaedic Hospital, P. Harrison (33; 0/33)
